JC02 Rec'd PCT/PTO 27 MAR 2002

FORM PTO-1390 (REV. 11-2000) — U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
0230-0174P	10/089179

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/06638	September 27, 2000	September 27, 1999

TITLE OF INVENTION
SEBUM PRODUCTION INHIBITORS

APPLICANT(S) FOR DO/EO/US
YATSUKA, Nobuaki; SATO, Nobuyuki; NISHIKAWA, Masazumi; TAMAI, Tadakazu; MORIYAMA, Shigeru

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau. WO 01/22971
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is transmitted herewith.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4)
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☒ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 20. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98, Form PTO-1449(s), and International Search Report (PCT/ISA/210) with 0 cited document(s).
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information:
    1.) PCT/IB/304 and PCT/IB/308
    2.) PCT/IPEA/409
    3.) Zero (0) sheets of Formal Drawings

JC13 Rec'd PCT/PTO 27 MAR 2002

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
10/NEW 089179	PCT/JP00/06638	0230-0174P

21. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. **$1,040.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO. **$740.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**		
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4). **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 0	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	7 - 20 =	0	X **$18.00**	$ 0	
Independent Claims	1 - 3 =	0	X **$84.00**	$ 0	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)		None	+ **$280.00**	$ 0	
			TOTAL OF ABOVE CALCULATIONS =	$ 890.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$ 0	
			SUBTOTAL =	$ 890.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐20 ☐30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0	
			TOTAL NATIONAL FEE =	$ 890.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 40.00	
			TOTAL FEES ENCLOSED =	$ 930.00	
			Amount to be: refunded	$	
			charged	$	

a. ☒ A check in the amount of $ **930.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account. No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2448.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to:
Birch, Stewart, Kolasch & Birch, LLP or Customer No. 2292
P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

Date: March 27, 2002

By _____ #36,623
Gerald M. Murphy, Jr., #28,977

/cgc

PATENT
0230-0174P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	YATSUKA, Nobuaki et al.		
Int'l. Appl. No.:	PCT/JP00/06638		
Appl. No.:	New	Group:	
Filed:	March 27, 2002	Examiner:	
For:	SEBUM PRODUCTION INHIBITORS		

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION
Assistant Commissioner for Patents
Washington, DC 20231

March 27, 2002

Sir:

The following Preliminary Amendments and Remarks are respectfully submitted in connection with the above-identified application.

AMENDMENTS

IN THE SPECIFICATION:

Please amend the specification as follows:

Before line 1, insert --This application is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/JP00/06638 which has an International filing date of September 27, 2000, which designated the United States of America.--

REMARKS

The specification has been amended to provide a cross-reference to the previously filed International Application.

Entry of the above amendments is earnestly solicited. An early and favorable first action on the merits is earnestly solicited.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By /M. Murphy #36,623
Gerald M. Murphy, Jr., #28,977

P.O. Box 747
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GMM/cqc
0230-0174P

(Rev. 11/13/01)

VERIFICATION OF A TRANSLATION

I, the below named translator, hereby declare that:

My name and post office address are as stated below;

That I am knowledgeable in the English language and in the language in which the below identified application was filed, and that I believe the English translation of International Application No. PCT/JP00/06638 is a true and complete translation of the above-identified International Application as filed.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated this 18th day of March, 2002

Full name of the translator: Hiroko EJIRI

Signature of the translator: Hiroko Ejiri

Post Office Address: c/o YUASA AND HARA, Section 206,
New Ohtemachi Bldg., 2-1,
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Tokyo, JAPAN

SPECIFICATION

SEBUM PRODUCTION INHIBITORS

TECHNICAL FIELD

The present invention relates to "sebum production inhibitors" containing as an active ingredient a compound having a glucuronic acid derivative and a glucosamine derivative in the structure.

BACKGROUND ART

The skin forms a thin sebaceous membrane on the surface of the epidermis. The sebaceous membrane plays the roles of preventing entry of outer foreign matters, protecting the skin against stimulation by various materials, smoothing the surface of the skin, inhibiting water evaporation, etc. However, it is known that excessive sebum is responsible for seborrheic diseases such as acne and dandruff. It is also known that sebum produces peroxides responsible for skin stimulation in the presence of UV rays or the like.

Acne is a typical seborrheic disease that is a skin disease mostly affecting teenagers and scientifically called acne vulgaris. It is clinically defined as "chronic inflammatory lesion prevailing the pilosebaceous system". Acne has not been etiologically explained yet, but it is considered as a skin disease caused by complex combination of various factors, among which excessive sebum production, keratinization at the follicle and follicular bacteria are generally thought to have important roles (for example,

Yamamoto Ayako: "Guidelines for Current Therapy, 1994 (Volume 36)", p. 632, Igaku-Shoin, Tokyo (1994)). Thus, common remedies for acne are external preparations containing sebum production inhibitors, keratolytic agents, antibacterials, lipase inhibitors and the like depending on the causative factor. However, acne remedies containing existing active ingredients have various disadvantages. For example, female hormones having a sebum production inhibitory effect inhibit epidermal growth to decrease sebum production, but hormone preparations induce undesirable side effects. Sulfur compounds such as sulfur and selenium disulfide representative of keratolytic agents do not show the hormone-like side effects, but often stimulate or dehydrate the skin during chronic use. Antibacterials such as hexachlorophenone, trichlorocarbanide and benzalkonium chloride show very high in vitro antimicrobial activity against the normal skin commensal, *Propionibacterium acnes*, but often show disappointing effects when they are actually used to treat acne in creams or ointments. Lipase inhibitors such as Ibuprofenpiconol or plant extracts such as peony or coptis root are not sufficiently effective for treating acne when they are formulated alone into creams or ointments.

A typical seborrheic disease in the scalp is increased dandruff. Excessive sebum is also considered to cause alopecia (Harada Shotaro: "Guidelines for Current Therapy, 1994 (Volume 36)", p. 633, Igaku-Shoin, Tokyo (1994); Watanabe Yasushi et al.: "Health Science, Diagnosis

List for Hair", p. 1, Japan Hair Science Association, Tokyo (1993)). It is thought that alopecia caused by increased dandruff or excessive sebum can be treated or prevented by inhibiting sebum production.

Excessive sebum production is also known to cause cosmetic problems such as rough skin, shiny skin and greasy skin or hair.

It is known that the causative agents for increased human body odor associated with aging are also derived from sebum (Asahi Shimbun (morning edition): August 30, 1999, p. 25). Any substances inhibiting sebum production may also control emission of the body odor associated with aging.

We already showed that compounds of the present invention have a platelet adhesion/aggregation suppressing effect in Japanese Patent Application No. 120425/1998 (JPA No. 310588/1999), a vascular endothelial cell growth promoting effect in Japanese Patent Application No. 273895/1998 (JPA No. 103738/2000) and a leukocyte-vascular endothelial cell adhesion suppressing effect in Japanese Patent Application No. 372864/1998 (JPA No. 191538/2000). However, any sebum production inhibitory effect has not been disclosed.

As evident from the above description, it is a medically and cosmetically important object to provide an excellent sebum production inhibitor.

DISCLOSURE OF THE INVENTION

As a result of careful studies to solve the above problems, we accomplished the present invention on the

basis of the finding that compounds of general formula (1) or pharmacologically acceptable salts thereof have an excellent sebum production inhibitory effect.

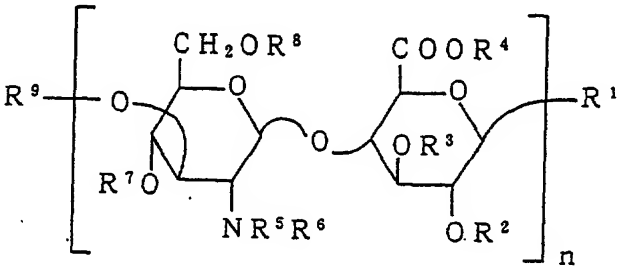
Accordingly, the present invention provides sebum production inhibitors containing as an active ingredient a compound of general formula (1) having a glucuronic acid derivative and a glucosamine derivative in the structure or a pharmacologically acceptable salt thereof.

Sebum production inhibitors of the present invention are useful as therapeutic or prophylactic agents for diseases caused by excessive sebum production. They are also useful as cosmetics for solving cosmetic problems caused by excessive sebum production. They are also useful as deodorants for the body odor associated with aging.

THE MOST PREFERRED EMBODIMENTS OF THE INVENTION

Compounds used in sebum production inhibitors of the present invention are compounds of general formula (1) below having a glucuronic acid derivative and a glucosamine derivative in the structure or pharmacologically acceptable salts thereof.

Formula (1)



where

R^1 denotes a protective group or any of formulae (2) to (5) below where R^{10} denotes a hydrogen atom, a protective group or any of formulae (6) to (8) below, and R^{11} denotes a hydrogen atom or a protective group, provided that when R^{10} and R^{11} are a hydrogen atom or a protective group, R^1 may be attached at the trans- or cis-position with respect to $COOR^4$,

Formula (2)

$-OR^{10}$

Formula (3)

$-NHR^{11}$,

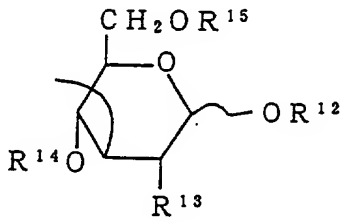
Formula (4)

$-CH_2R^{11}$,

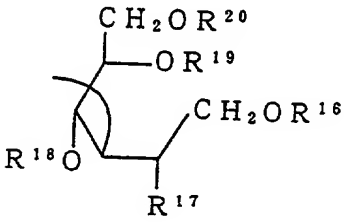
Formula (5)

$-SR^{11}$,

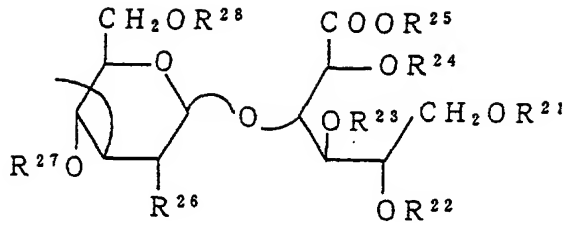
Formula (6)



Formula (7)



Formula (8)



or when R^{10} is any of formulae (6) to (8), R^{12} to R^{28} except R^{13}, R^{17} and R^{26} in formulae (6) to (8) are the same or different and denote a hydrogen atom or a protective group, and R^{13}, R^{17} and R^{26} denote an azido group or formula (9) below

Formula (9)

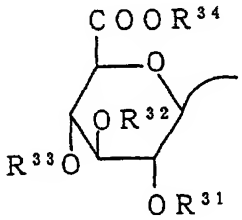
$$-NR^{29}R^{30}$$

where R^{29} and R^{30} are the same or different and denote a hydrogen atom or a protective group,

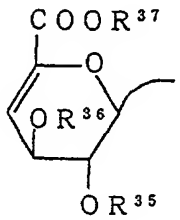
R^2 to R^8 are the same or different and denote a hydrogen atom or a protective group,

R^9 denotes a hydrogen atom, a protective group or formula (10) or (11) below

Formula (10)



Formula (11)



where R^{31} to R^{37} are the same or different and denote a hydrogen atom or a protective group, and

n denotes an integer of 0 to 25, provided that when n is 0, R^1 is a group of formula (2), R^{10} is a group of formula (8), and R^9 is a group of formula (10) or (11),

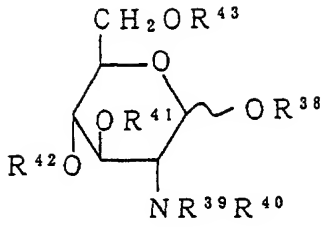
with the proviso that in formulae (1), (6) to (8), and (10) to (11), the protective groups are the same or different and denote an optionally substituted straight or branched alkyl having 1 to 8 carbon atoms, an optionally substituted straight or branched alkenyl having 2 to 8 carbon atoms, an optionally substituted acyl having 1 to 8 carbon atoms, an optionally substituted aromatic acyl, or an optionally substituted aromatic alkyl,

or any two protective groups of R^2 to R^{37} except R^{13}, R^{17} and R^{26} may be combined to form an optionally substituted alkylidene having 3 to 8 carbon atoms, an optionally substituted cyclic alkylidene having 3 to 8 carbon atoms, optionally substituted benzylidene or optionally substituted phthaloyl, and

when n is 2 or more, R^2 to R^8 may be the same or different in each recurring unit.

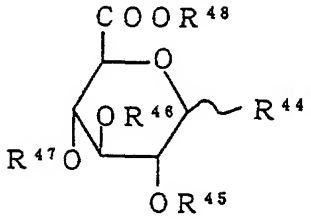
That is, compounds of formula (1) contained as active ingredients in sebum production inhibitors of the invention have a structure comprising a D-glucosamine derivative of formula (12) below and a D-glucuronic acid derivative of formula (13) below combined together.

Formula (12)



where R^{38} to R^{43} denote a hydrogen atom or a protective group.

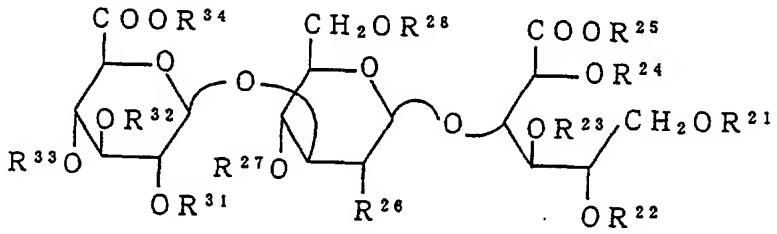
Formula (13)



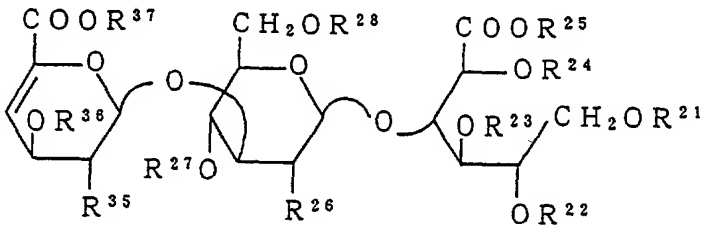
where R^{44} denotes a hydroxyl group or a protective group, and R^{45} to R^{48} denote a hydrogen atom or a protective group.

In formula (1), n denotes an integer of 0 to 25, provided that when n is 0, R^1 is a group of formula (8) and R^9 is a group of formula (10) or (11). That is, compounds of formula (1) are represented by formula (14) or (15) below.

Formula (14)



Formula (15)



As used herein, the protective group includes various protective groups shown in Theodra W. Green: "Productive Groups in Organic Synthesis"; 2nd Ed.; 1991.

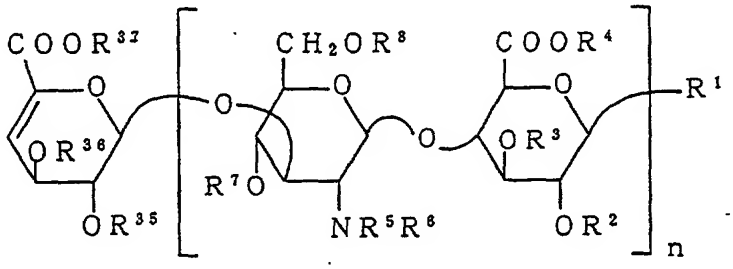
The protective groups shown in formulae (1) to (11) above include optionally substituted straight or branched alkyls having 1 to 8 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, tertiary butyl, pentyl, octyl, methoxymethyl, tertiary butylthiomethyl, 1-ethoxyethyl, siloxymethyl or 2-methoxyethoxymethyl; optionally substituted straight or branched alkenyls having 2 to 8 carbon atoms such as ethenyl, 1-propenyl, 2-propenyl, butenyl or octenyl; optionally substituted straight or branched acyls having 1 to 8 carbon atoms such as formyl, acetyl, propionyl, butyryl, valeryl or pivaloyl, or haloacyls including chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl; optionally substituted aromatic acyls such as benzoyl or parachlorobenzoyl; optionally substituted aromatic alkyls such as optionally substituted benzyl (e.g., 4-methoxybenzyl), optionally substituted diphenylmethyl or optionally substituted triphenylmethyl. As for the protective groups shown in formulae (1) to (11), any two protective groups of R^2 to R^{37}

except R^{13}, R^{17} and R^{26} may be combined to form a protective group, i.e., suitable protective groups further include optionally substituted alkylidenes having 3 to 8 carbon atoms such as propylidene, butylidene or octylidene; optionally substituted cyclic alkylidenes having 3 to 8 carbon atoms such as cyclopentylidene, cyclohexylidene or cycloheptylidene; and optionally substituted benzylidene or optionally substituted phthaloyl. Preferred protective groups for hydroxyl group include optionally substituted straight or branched acyls having 1 to 8 carbon atoms, optionally substituted aromatic alkyls, optionally substituted straight or branched alkenyls having 2 or more carbon atoms, or optionally substituted benzylidene, more preferably acetyl, benzyl, 1-propenyl or benzylidene. Preferred protective groups for amino group include optionally substituted straight or branched acyls having 1 to 8 carbon atoms or optionally substituted phthaloyl, more preferably acetyl or phthaloyl. Preferred protective groups for carboxyl group include optionally substituted straight or branched alkyls having 1 to 8 carbon atoms or optionally substituted aromatic alkyls, more preferably methoxyl, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl or diphenylmethyl. The protective groups mentioned above may be the same or different in the same compound, and can be selected arbitrarily.

In formula (1), n is an integer of 0 to 25, preferably 0 to 10, more preferably 0 to 5, most preferably 2 to 4.

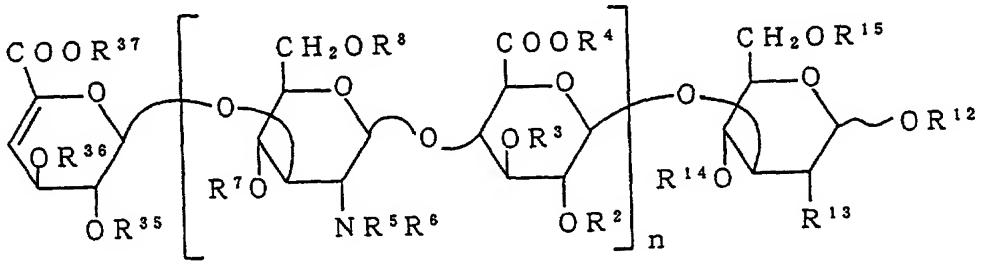
R^9 may be as defined above, and is preferably represented by formula (11). That is, compounds of formula (1) are preferably represented by formula (16) below.

Formula (16)

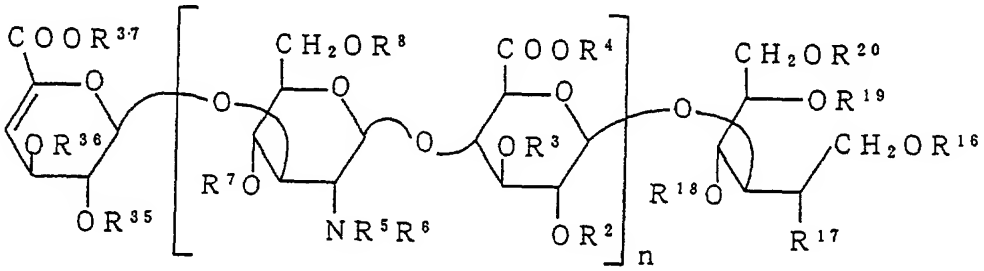


More preferably, R^1 in formula (11) is represented by any of formulae (6) to (8), i.e., compounds are represented by any of formulae (17) to (19) below.

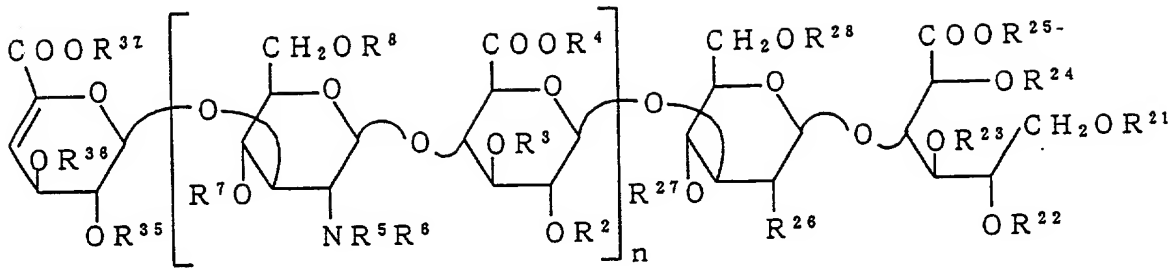
Formula (17)



Formula (18)



Formula (19)



Most preferably, R^{13}, R^{17} and R^{26} in formulae (17) to (19) above are represented by formula (9) above.

As used herein, the pharmacologically acceptable salt refers to a salt that has no adverse influence in vivo when a compound of the invention is administered in a therapeutically or prophylactically necessary amount, or a salt that does not lose pharmacologically effective properties of a compound of the invention. Specific examples are salts of alkali or alkali earth metals such as sodium salts, potassium salts or calcium salts; hydrohalogenic acid salts such as hydrofluorides, hydrochlorides, hydrobromides and hydroiodides; lower alkylsulfonates such as methanesulfonates, trifluoromethanesulfonates and ethanesulfonates; arylsulfonates such as benzenesulfonates and p-toluenesulfonates; organic acid salts such as fumarates, succinates, citrates, tartrates, oxalates and maleates; and amino acid salts such as glutamates and aspartates. Compounds of the invention and their salts also include solvates with various pharmacologically acceptable solvents such as water, organic solvents and buffers, or polymorphic

forms.

Compounds of formula (1) may have an asymmetric carbon atom, depending on the type of the substituent, and may exist as optical isomers based on the presence of the asymmetric center. Thus, compounds of the present invention include all of individual isomers and their mixtures. For example, mixtures of an optical isomer and its enantiomer, especially racemic modifications consisting of a mixture of equal amounts of D and L isomers, or mixtures of an optical isomer and its diastereomer are included.

[Methods for producing compounds of formula (1)]

Needless to say, various methods are available for obtaining compounds used in sebum production inhibitors of the invention. Examples of such methods are organic chemical methods, namely methods of synthesizing or modifying intermediates or desired compounds by organic chemical techniques using glucuronic acid derivatives and glucosamine derivatives as starting materials, or methods of obtaining intermediates or desired compounds by decomposing polysaccharides with acids or alkalis; biochemical methods, namely methods of synthesizing or modifying intermediates or desired compounds by utilizing reverse reactions of transferases or depolymerization enzymes with the use of glucuronic acid and N-acetylglucosamine as starting materials, or methods of obtaining intermediates or desired compounds by depolymerizating polysaccharides with enzymes; and genetic

engineering methods, namely methods of obtaining starting materials, intermediates or desired compounds, or enzymes for use in synthesis or modification, by introduction of genes for enzymes into microorganisms or cells. These methods are used alone or in combination.

Preferred processes for preparing compounds of formula (1) are described in detail in Japanese Patent Application No. 120425/1998 (JPA No. 310588/1999) mentioned above.

[Sebum production inhibitors of the present invention and administration modes, doses and dosage forms thereof]

Sebum production inhibitors of the present invention contain as an active ingredient at least one of compounds of formula (1) or pharmacologically acceptable salts thereof.

When sebum production inhibitors of the present invention are used as medicines or cosmetics, they are normally administered systemically or locally, orally or parenterally. The dose is not specifically limited but should be optimally determined on the basis of overall judgment depending on various factors such as the type of the disease, the severity of the condition, the age and body weight of the subject to be treated. However, the daily dose is normally 0.01 to 100 mg/kg orally or 0.001 to 10 mg/kg parenterally per adult. The dose is administered once daily or divided into subdoses depending on the purpose.

Compounds of the present invention may be administered orally in the form of solid compositions, liquid compositions and other compositions or parenterally

in the form of injections, external preparations and suppositories, and an optimal administration mode is selected depending on the purpose. Pharmaceutical compositions containing as an active ingredient at least one of compounds of the present invention and pharmacologically acceptable salts thereof can be prepared by using carriers, excipients and other additives used for ordinary formulation. Suitable carriers and excipients for formulation include, for example, lactose, magnesium stearate, starch, talc, gelatin, agar, pectin, acacia, olive oil, sesame oil, cacao butter, ethylene glycol and other common additives.

Suitable solid compositions for oral administration include tablets, pills, capsules, powders and granules. In such solid compositions, at least one active substance (active ingredient) is mixed with at least one inert diluent, such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, or magnesium aluminometasilicate. The compositions may conventionally contain additives other than inert diluents, for example, lubricants such as magnesium stearate, disintegrants such as calcium carboxymethylcellulose, and solubilizers such as glutamic acid or aspartic acid. Tablets or pills may, if desired, be coated with a sugar coating or a gastric or enteric film comprising sucrose, gelatin, hydroxypropyl methylcellulose phthalate or the like or may be coated with two or more layers. Capsules of an absorbable material such as gelatin

are also included.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs, and may contain ordinary inert diluents, such as purified water and ethanol. In addition to inert diluents, these compositions may contain adjuvants such as wetting agents or suspending agents, sweetening agents, flavoring agents, aromatics and preservatives.

Injections for parenteral administration include sterile aqueous or nonaqueous solutions, suspensions and emulsions. Aqueous solutions and suspensions contain water for injection and physiological saline for injection, for example. Nonaqueous solutions and suspensions contain propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohols such as ethanol, and POLYSORBATE 80 (registered trademark). These compositions may further contain adjuvants, such as preservatives, wetting agents, emulsifying agents, dispersing agents, stabilizers (e.g., lactose), and solubilizers (e.g., glutamic acid and aspartic acid). These can be sterilized by ordinary sterilizing methods, such as mechanical sterilization with a microfiltration membrane, heat sterilization such as autoclaving or inclusion of a bactericide. It is also possible to prepare a sterile solid composition and dissolve it in sterile water or a sterile solvent for injection before use.

Pharmaceutical compositions for parenteral

administration or cosmetics include liquid preparations for external use, ointments, liniments, suppositories, transdermal preparations and ophthalmic solutions containing at least one of compounds of the present invention as an active ingredient. They can also be used in the form of oil-absorbing sheets or films. Formulations and preparation processes of various forms of cosmetics are described in known documents such as "Modern Cosmetic Science" (edited by Cosmetic Science Institute, Yakuji Nippo, 1980).

[Sebum synthesis inhibitory effect of compounds of formula (1)]

Compounds of the present invention (Compound Nos. 1-10) were evaluated for sebum production inhibitory effect on hamster auricular skin tissue sections containing sebaceous glands. As a result, the compounds of the present invention showed an excellent sebum production inhibitory effect.

INDUSTRIAL APPLICABILITY

Compounds of formula (1) and pharmacologically acceptable salts thereof have an excellent sebum synthesis inhibitory effect so that they are useful as therapeutic and prophylactic agents based on such an effect. Specifically, they are useful as therapeutic and prophylactic agents for acne, dandruff, alopecia, etc.

They are also useful as ingredients of cosmetics. Specifically, they are useful as cosmetics for preventing rough skin, shiny skin, greasy skin or hair, the body odor

associated with aging, etc.

Examples

The following examples further illustrate the present invention by way of Compound Production Examples, Test Examples for Sebum Production Inhibitory Effect, and Preparation Examples of Formulations and Cosmetics. As a matter of course, the invention is not limited to the materials and formulations described in the following examples, but includes all the materials and formulations included in the scope of claims.

Example 1: Compound Production Example 1

Production of 4-deoxy-α-L-threo-hexa-4-enepyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranose [ΔHexA β1→3GlcNAc β1→4GlcA β1→3GlcNAc (Compound Example 1)], 4-deoxy-α-L-threo-hexa-4-enepyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranose [ΔHexA β1→3GlcNAc β1→4GlcA β1→3GlcNAc β1→4GlcA β1→3GlcNAc (Compound Example 2)], 4-deoxy-α-L-threo-hexa-4-enepyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranose [ΔHexA β1→3GlcNAc

β1→4GlcA β1→3GlcNAc β1→4GlcA β1→3GlcNAc β1→4GlcA β1→3GlcNAc (Compound Example 3)], and 4-deoxy-α-L-threo-hexa-4-enepyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranose [ΔHexA β1→3GlcNAc β1→4GlcA β1→3GlcNAc β1→4GlcA β1→3GlcNAc β1→4GlcA β1→3GlcNAc β1→4GlcA β1→3GlcNAc (Compound Example 4)]

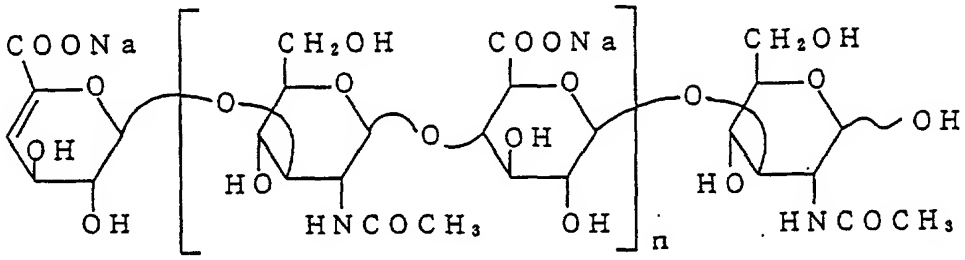
A solution of 30 g of sodium hyaluronate (a product of KIBUN FOOD CHEMIFA; trade name "Hyaluronic acid FCH") dissolved in 3L of distilled water was heated to 40°C. The solution was adjusted to pH 6.0 with 0.1 M aqueous sodium hydroxide solution, and then a hyaluronidase derived from Streptomyces hyalurolyticus (a product of Amano Pharmaceutical; trade name "Hyaluronidase "Amano"") was added to decrease 0.5 turbidity units per mg of sodium hyaluronate, and the mixed solution was reacted for 100 hours at 40°C. After the reaction, the enzyme was removed from the solution by an ultrafiltration membrane (a product of Millipore) of hydrophilic polyether sulfone with a nominal molecular weight cutoff of 10k. The solvent was removed by lyophilization to give a depolymerization product (27.4 g).

The depolymerization product was fractionated by

anion exchange chromatography (column: YMC-Pack IEC-AX, eluent A: water, B: 0.4M NaCl; linear gradient (30 min), detection: UV (232 nm)) (Compound Examples 1, 2, 3 and 4 were eluted in this order) to obtain fractions containing Compound Examples 1 to 4. Each fraction was desalted by gel filtration (gel: Sephadex G-10, eluent: water), and then lyophilized to obtain Compound Nos. 1 to 4 (white powder). Yields: Compound Example 1: 1.7 g, Compound Example 2: 5.9 g, Compound Example 3: 3.4 g, Compound Example 4: 2.2 g. Each compound was obtained as a sodium salt.

Compound Examples 1 to 4 are represented by formula (20) below where n denotes an integer of 1 to 4, i.e., n is 1, 2, 3 and 4, respectively.

Formula (20)



The purity of each compound measured by high performance liquid chromatography (column: TSKgel DEAE-5PW, eluent A: water, B: 0.3M NaCl; linear gradient (20 min), detection: UV (232 nm); area percentage method) was 97% or more. For each compound, the uronic acid content analyzed by the method of Bitter and Muir (Bitter, T., Muir, H.: Anal. Biochem., 4, 330 (1962)) using glucuronolactone as a

standard and the hexosamine content analyzed by the method of Boas (without resin treatment; Boas, N., F.: J. Biol. Chem., 204, 553 (1953).) using glucosamine hydrochloride as a standard after hydrolysis at 100°C for 16 hours in 3N hydrochloric acid nearly agreed with the theoretical values.

Example 2: Compound Production Example 2

Production of 4-deoxy-α-L-threo-hexa-4-enepyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranose [ΔHexA β1→3GlcNAc β1→4GlcA β1→3GlcNAc (Compound Example 1)], and 4-deoxy-α-L-threo-hexa-4-enepyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranose [ΔHexA β1→3GlcNAc β1→4GlcA β1→3GlcNAc β1→4GlcA β1→3GlcNAc (Compound Example 2)]

A solution of 60 g of sodium hyaluronate (a product of KIBUN FOOD CHEMIFA; trade name "Hyaluronic acid FCH") dissolved in 3L of distilled water was heated to 40°C. The solution was adjusted to pH 6.0 with 0.1 M aqueous sodium hydroxide solution, and then a hyaluronidase derived from *Streptomyces hyalurolyticus* (a product of Amano Pharmaceutical; trade name "Hyaluronidase "Amano"") was added to decrease 1 turbidity unit per mg of sodium hyaluronate, and the mixed solution was reacted for 100 hours at 40°C. After the reaction, the enzyme was removed from the solution by an ultrafiltration membrane (a product

of Millipore) of hydrophilic polyethersulfone with a nominal molecular weight cutoff of 10k. The solvent was removed by lyophilization to give a depolymerization product (53.7 g).

The depolymerization product was fractionated by anion exchange chromatography (column: TSKgel DEAE-5PW, eluent A: water, B: aqueous solution of 0.5M sodium acetate; linear gradient (A/B (90/10) → A/B (60/40); 40 min), detection: UV (232 nm)) (Compound Examples 1 and 2 were eluted in this order) to obtain fractions containing Compound Examples 1 and 2. Each fraction was lyophilized to remove water. Each lyophilized fraction was desalted by washing with ethanol to give Compound Examples 1 and 2 (white powder). Yields: Compound Example 1: 18.1 g, Compound Example 2: 29.5 g. Each compound was obtained as a sodium salt.

The purity of each compound measured by high performance liquid chromatography (column: TSKgel Amide-80, eluent: acetonitrile/water/acetic acid/triethylamine (65/35/2/1, v/v), flow velocity: 1.0 mL/min, column temperature: 80°C, detection: UV (232 nm); area percentage method) was 97% or more. The uronic acid content and hexosamine content analyzed by the methods shown in Example 1 nearly agreed with the theoretical values.

Example 3: Compound Production Example 3

Production of 4-deoxy-α-L-threo-hexa-4-enepyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-

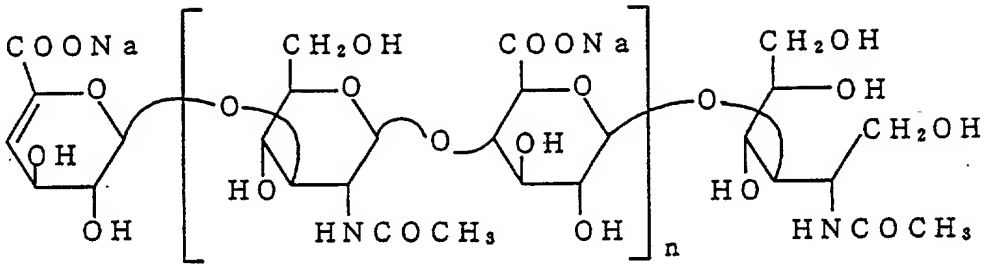
acetamide-2-deoxy-β-D-glucopyranitol [ΔHexA β1→3GlcNAc β1→4GlcA β1→3GlcNAc OH (Compound Example 5)], and 4-deoxy-α-L-threo-hexa-4-enepyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranitol [ΔHexA β1→3GlcNAc β1→4GlcA β1→3GlcNAc β1→4GlcA β1→3GlcNAc OH (Compound Example 6)]

A solution of 50 mg of Compound Example 1 dissolved in 50 mL of an aqueous solution of 3 mg/mL sodium borohydride was treated for 1 hour at room temperature. The reaction was quenched with 5 mL of 6 M acetic acid and 50 mL of methanol was added, and then the mixture was dried on an evaporator. The addition of 50 mL methanol and evaporation were further repeated twice. The solid remaining after evaporation was dissolved in 5 mL of water and the solution was desalted by gel filtration in the same manner as in Example 1, and then lyophilized to give Compound Example 5 (white powder: 44.7 mg).

In the same manner, Compound Example 6 was obtained using Compound Example 2 as the starting material.

Compound Examples 5 and 6 are represented by formula (21) where n denotes an integer of 1 to 2, i.e., n is 1 and 2, respectively.

Formula (21)



The purity of each of Compound Nos. 5 and 6 measured by the method shown in Example 2 was 98% or higher. The uronic acid content and hexosamine content analyzed by the methods shown in Example 1 nearly agreed with the theoretical values.

Example 4: Compound Production Example 4

Production of 4-deoxy-α-L-threo-hexa-4-enepyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronic acid [ΔHexA β1→3GlcNAc β1→4GlcA (Compound Example 7)], and 4-deoxy-α-L-threo-hexa-4-enepyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronic acid [ΔHexA β1→3GlcNAc β1→4GlcA β1→3GlcNAc β1→4GlcA (Compound Example 8)]

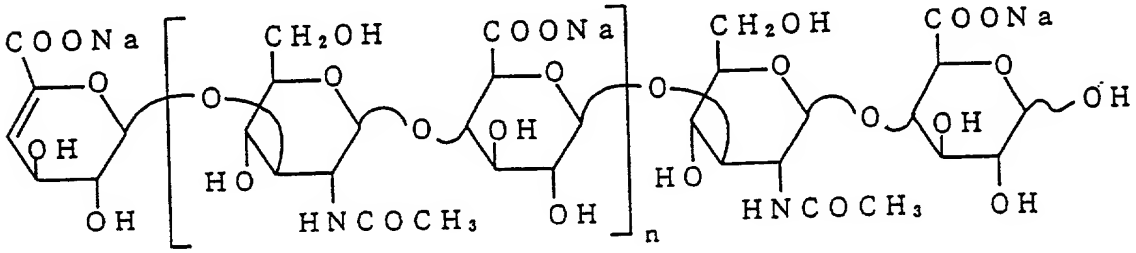
Compound Example 1 was heated in a borate buffer at pH 9 in accordance with the method of Reissig et al. (Reissig, J., L., Strominger, J. L., Leloir, L., F.: J. Biol. Chem., 217, 959 (1953).). Boric acid in the reaction mixture was removed as methyl borate in the same manner as in Example 3. The remaining mixture was desalted by gel

filtration in the same manner as in Example 1, and then lyophilized to obtain Compound Example 7 (white powder). Starting from 50 mg of Compound Example 1, 43.1 mg of Compound Example 7 was obtained.

Similarly, 44.8 mg of Compound Example 8 (white powder) was obtained starting from 50 mg of Compound Example 2.

Compound Examples 7 and 8 are represented by formula (22) where n denotes an integer of 0 to 1, i.e., n is 0 and 1, respectively.

Formula (22)



The purity of each of Compound Examples 7 and 8 measured by the method shown in Example 2 was 98% or higher. The uronic acid content and hexosamine content analyzed by the methods shown in Example 1 nearly agreed with the theoretical values.

Example 5: Compound Production Example 5

Production of 4-deoxy-α-L-threo-hexa-4-enepyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronitol [ΔHexA β1→3GlcNAc β1→4GlcA OH (Compound Example 9)], and 4-deoxy-α-L-threo-hexa-4-enepyranuronosyl-(1→3)-O-2-acetamide-2-

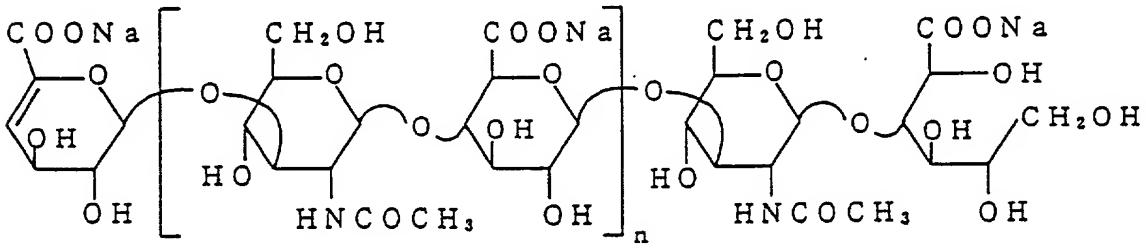
deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronosyl-(1→3)-O-2-acetamide-2-deoxy-β-D-glucopyranosyl-(1→4)-3-O-β-D-glucopyranuronitol [ΔHexA β1→3GlcNAc β1→4GlcA β1→3GlcNAc β1→4GlcA OH (Compound Example 10)]

Compound Example 7 was treated in the same manner as in Example 3 to give Compound Example 9 (white powder). Starting from 20 mg of Compound Example 7, 15.9 mg of Compound Example 9 was obtained.

Similarly, 17.8 mg of Compound Example 10 (white powder) was obtained starting from 20 mg of Compound Example 8.

Compound Examples 9 and 10 are represented by formula (23) where n denotes an integer of 0 to 1, i.e., n is 0 and 1, respectively.

Formula (23)



The purity of each of Compound Nos. 9 and 10 measured by the method shown in Example 2 was 98% or higher. The uronic acid content and hexosamine content analyzed by the methods shown in Example 1 nearly agreed with the theoretical values.

Example 6: Sebum production inhibitory effect of compounds of formula (1)

The method of Hall et al. (Hall, D.W.R., Van den Hoven, W.E., Noordzij-Kamermans, N.J., Jaitly, K.D., Arch. Dermatol. Res., 275, 1 (1983)) was followed. Namely, male hamster auricular skin tissue sections (3 mm in diameter) containing sebaceous glands were cultured for 3 hours in Krebs-Ringer phosphate buffer containing radioactively labeled sodium acetate, and then tissues were hydrolyzed and extracted with hexane. The radioactively labeled fat levels in hexane were measured in a liquid scintillation counter to determine fat production inhibition levels in sebaceous glands. Skin tissues isolated from the right auricula were cultured in Krebs-Ringer phosphate buffer containing 0.01% or 0.05% of compounds of the present invention (Compound Nos. 1-10) (compound systems), while skin tissues from the left auricula of the same hamster were cultured in Krebs-Ringer phosphate buffer containing no compounds of the present invention (control system). The sebum production inhibition percentage was calculated by the equation below from the test data obtained.

Sebum production inhibition (%) =

[(Sebum production level in control system) -
(Sebum production level in each compound system)] /
(Sebum production level in control system) x 100

The results are shown in Table 1.

Table 1

Compound No.	Sebum production inhibition (%)	
	Concentration of compound in the medium (%)	
	0.01	0.05
1	15.7	17.8
2	28.6	50.1
3	48.5	47.7
4	53.4	51.0
5	16.2	18.1
6	30.8	55.7
7	14.2	15.9
8	30.7	56.6
9	13.9	20.0
10	39.8	55.1

As shown in Table 1, all of Compound Nos. 1-10 were found to significantly inhibit fat production from skin tissue sections containing sebaceous glands and therefore have an excellent sebum production inhibitory effect.

Example 7: Acute toxicity of compounds of the present invention

Representative examples of compounds of the present invention (Compound Nos. 1-10) were tested for acute toxicity on rats (body weight 300-400 g, Wistar, male) to show LD_{50} of 500 mg/kg or more.

Example 8: Preparation example of formulations and cosmetics

Preparation of tablet 1

Compound Example 1	10 g
Polyethylene glycol 6000	10 g
Sodium lauryl sulfate	1.5 g
Corn starch	3 g
Lactose	25 g
Magnesium stearate	0.5 g

The above ingredients are weighed. Polyethylene glycol 6000 is heated to 70 to 80°C, and mixed with Compound Example 1, sodium lauryl sulfate, corn starch, and lactose, followed by cooling. The solidified mixture is granulated by means of a grinder to obtain granules. The granules are mixed with magnesium stearate, and then compressed into tablets with a weight of 250 mg.

Preparation of tablet 2

Compound Example 2	30 g
Lactose	55 g
Potato starch	12 g
Polyvinyl alcohol	1.5 g
Magnesium stearate	1.5 g

The above ingredients are weighed. Compound Example 2, lactose and potato starch are uniformly mixed. An aqueous solution of polyvinyl alcohol is added to the mixture, and the mixed solution is wet granulated. The resulting granules are dried and mixed with magnesium stearate. Then, the mixture is compressed into tablets with a weight of 200 mg.

Preparation of capsule

Compound Example 3	10 g

Lactose	25 g
Corn starch	5 g
Microcrystalline cellulose	9.5 g
Magnesium stearate	0.5 g

The above ingredients are weighed. The four ingredients except magnesium stearate are uniformly mixed. Magnesium stearate is added, and then the ingredients are further mixed for several minutes. The mixture is filled into No. 1 hard capsule shells in an amount of 200 mg/capsule to form capsules.

Preparation of powder

Compound Example 4	20 g
Lactose	79 g
Magnesium stearate	1 g

The above ingredients are weighed. All the ingredients are uniformly mixed to form a 20% powder.

Preparation of suppository

Compound Example 5	10 g
Polyethylene glycol 1500	18 g
Polyethylene glycol 4000	72 g

Compound Example 2 is thoroughly ground in a mortar to form a fine powder, and made into a 1 g rectal suppository by a melting method.

Preparation of injection

Compound Example 6	0.1 g
Sodium chloride	0.9 g
Sodium hydroxide	Suitable amount
Water for injection	100 mL

The above ingredients are weighed. The three ingredients are dissolved in water for injection, and the solution is sterilized by filtration. Then, the solution is dispensed into 10 mL ampoules in an amount of 5 mL per ampoule. The ampoule is heat sealed to form an injection.

Preparation of cream

Compound Example 7	5 g
Cetostearyl alcohol	3.5 g
2-Octyldodecyl alcohol	3 g
Squalane	40 g
Beeswax	3 g
Reduced lanolin	5 g
Ethylparaben	0.3 g
Polyoxyethylene (20) sorbitan monopalmitate ester	2 g
Monoglyceride stearate	2 g
Perfume	0.03 g
1,3-Butylene glycol	5 g
Glycerin	5 g
Purified water	26.2 g

The above ingredients are weighed and formulated into a cream by a standard procedure.

Preparation of emulsion

Compound Example 8	1 g
Liquid paraffin	5 g
Stearic acid	1.5 g
Cetyl alcohol	0.5 g
Beeswax	2 g

Isopropyl myristate	3 g
Polyoxyethylene (10) monooleate ester	1 g
Glyceryl monostearate ester	1 g
Propylene glycol	5 g
Ethanol	3 g
Ethylparaben	0.3 g
Perfume	0.03 g
Purified water	76.7 g

The above ingredients are weighed and formulated into an emulsion by a standard procedure.

Preparation of ointment

Compound Example 9	0.1 g
Stearyl alcohol	15 g
Japan wax	20 g
Polyoxyethylene (10) monooleate ester	0.25 g
Glyceryl monostearate ester	0.25 g
Vaseline	40 g
Purified water	24.4 g

The above ingredients are weighed and formulated into an ointment by a standard procedure.

Preparation of pack

Compound Example 10	7 g
Polyvinyl alcohol	15 g
Dipropylene glycol	5 g
Polyethylene glycol	3 g
Ethanol	10 g
Methylparaben	0.05 g
Perfume	0.05 g

Purified water	59.9 g

The above ingredients are weighed and formulated into a pack by a standard procedure.

Preparation of pressed powder

Compound Example 2	1 g
Talc	85.4 g
Stearic acid	1.5 g
Lanolin	5 g
Squalane	5 g
Sorbitan sesquioleate ester	2 g
Triethanolamine	1 g
Pigment	q.s.
Perfume	q.s.

The above ingredients are weighed and formulated into a pressed powder by a standard procedure.

Preparation of hair tonic

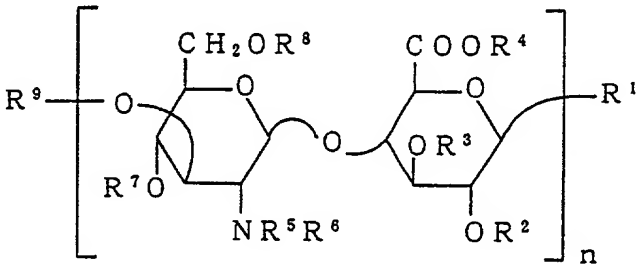
Compound Example 3	1 g
Ethanol	55 g
Nikkol HCO-60	1 g
Perfume	q.s.
Purified water	42 g
Glycerin	1 g
Dye	q.s.

The above ingredients are weighed and formulated into a hair tonic by a standard procedure.

CLAIMS

1. A sebum production inhibitor containing as an active ingredient a compound of general formula (1) below having a glucuronic acid derivative and a glucosamine derivative in the structure or a pharmacologically acceptable salt thereof.

Formula (1)



where

R^1 denotes a protective group or any of formulae (2) to (5) below where R^{10} denotes a hydrogen atom, a protective group or any of formulae (6) to (8) below, and R^{11} denotes a hydrogen atom or a protective group, provided that when R^{10} and R^{11} are a hydrogen atom or a protective group, R^1 may be attached at the trans- or cis-position with respect to $COOR^4$,

Formula (2)

$-OR^{10}$

Formula (3)

$-NHR^{11}$,

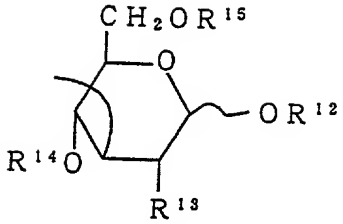
Formula (4)

$-CH_2R^{11}$,

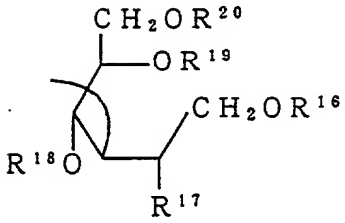
Formula (5)

$-SR^{11}$,

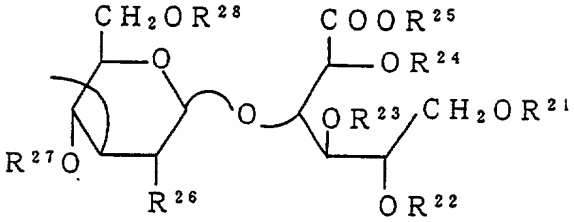
Formula (6)



Formula (7)



Formula (8)



or when R^{10} is any of formulae (6) to (8), R^{12} to R^{28} except R^{13}, R^{17} and R^{26} in formulae (6) to (8) are the same or different and denote a hydrogen atom or a protective group, and R^{13}, R^{17} and R^{26} denote an azido group or formula (9) below

Formula (9)

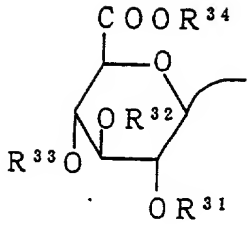
$-NR^{29}R^{30}$

where R^{29} and R^{30} are the same or different and denote a hydrogen atom or a protective group,

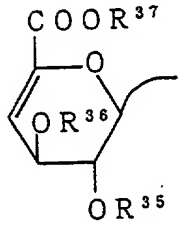
R^2 to R^8 are the same or different and denote a hydrogen atom or a protective group,

R^9 denotes a hydrogen atom, a protective group or formula (10) or (11) below

Formula (10)



Formula (11)



where R^{31} to R^{37} are the same or different and denote a hydrogen atom or a protective group, and

n denotes an integer of 0 to 25, provided that when n is 0, R^1 is a group of formula (2), R^{10} is a group of formula (8), and R^9 is a group of formula (10) or (11),

with the proviso that in formulae (1), (6) to (8), and (10) to (11), the protective groups are the same or different and denote an optionally substituted straight or branched alkyl having 1 to 8 carbon atoms, an optionally substituted straight or branched alkenyl having 2 to 8 carbon atoms, an optionally substituted acyl having 1 to 8 carbon atoms, an optionally substituted aromatic acyl, or an optionally substituted aromatic alkyl,

or any two protective groups of R^2 to R^{37} except R^{13}, R^{17} and R^{26} may be combined to form an optionally substituted alkylidene having 3 to 8 carbon atoms, an optionally substituted cyclic alkylidene having 3 to 8 carbon atoms, optionally substituted benzylidene or optionally

substituted phthaloyl, and

when n is 2 or more, R^2 to R^8 may be the same or different in each recurring unit.

2. The sebum production inhibitor of claim 1 for use as a therapeutic or prophylactic agent for diseases caused by excessive sebum production.

3. The sebum production inhibitor of claim 2, which is a therapeutic or prophylactic agent for acne vulgaris.

4. The sebum production inhibitor of claim 2, which is a therapeutic or prophylactic agent for dandruff.

5. The sebum production inhibitor of claim 2, which is a therapeutic or prophylactic agent for alopecia.

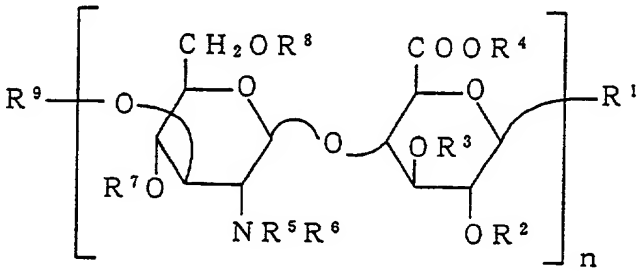
6. The sebum production inhibitor of claim 1 for use as a cosmetic for solving cosmetic problems caused by excessive sebum production.

7. The sebum production inhibitor of claim 1 for use as a deodorant for the body odor associated with aging.

ABSTRACT

Sebum production inhibitors containing as an active ingredient a compound of general formula (1) below having a glucuronic acid derivative and a glucosamine derivative in the structure or a pharmacologically acceptable salt thereof.

Formula (1)



BIRCH, STEWART, KOLASCH & BIRCH, LLP

PLEASE NOTE: YOU MUST COMPLETE THE FOLLOWING:

COMBINED DECLARATION AND POWER OF ATTORNEY FOR PATENT AND DESIGN APPLICATIONS

ATTORNEY DOCKET NO. 0230-0174P

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Insert Title: SEBUM PRODUCTION INHIBITORS

Fill in Appropriate Information - For Use Without Specification Attached:

the specification of which is attached hereto. If not attached hereto,

the specification was filed on _____ as United States Application Number _____; and /or

the specification was filed on September 27, 2000 as PCT International Application Number PCT/JP00/06638; and was amended under PCT Article 19 on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Insert Priority Information: (if appropriate)

Prior Foreign Application(s)

(Number)	(Country)	(Month/Day/Year Filed)	Priority Claimed
272022/1999	Japan	9/27/1999	☒ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

Insert Provisional Application(s): (if any)

(Application Number)	(Filing Date)

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More Than 12 Months (6 Months for Designs) Prior To The Filing Date of This Application:

Insert Requested Information: (if appropriate)

Country	Application No.	Date of Filing (Month/Day/Year)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Insert Prior U.S. Application(s): (if any)

(Application Number)	(Filing Date)	(Status - patented, pending, abandoned)

I hereby appoint the following attorneys to prosecute this application and/or an international application based on this application and to transact all business in the Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the attorneys identified below, unless the inventor(s) or assignee provides said attorneys with a written notice to the contrary: Atty Dckt No.: 0230-0174P

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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* DATE OF SIGNATURE

(USPTO Approved 3-90)
(Revised 8-97)